REMARKS/ARGUMENTS

After entry of this paper, claims 13-16, 18, and 31-39 are pending. Claims 13 and 15 are amended to clarify the invention. These amendments are supported throughout the specification and add no new matter.

Rejection

Claims 13-16, 18, and 31-39 are rejected under 35 USC §103(a) as allegedly being unpatentable over Skotnicki (US Patent No. 5,362,718) in view of Waranis (US Patent No. 5,516,770) and Haeberlin (Great Britain Patent Publication No. 2,327,611).

The Examiner alleged that "...it is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art" by referencing In re Aller.

The Examiner also alleged that it would have been obvious to one of skill in the art to combine:

- *Skotnicki's teachings of hydroxyester rapamycin derivatives and formulations thereof;*
- *Waranis' teachings of solvent, rapamycin, and polysorbate 80 concentrations to provide a parenteral rapamycin formulation;*
- *Haeberlin's teachings of the instability of rapamycins and the need to use citric acid and d,l-α-tocopherol as a stabilizer in a rapamycin parenteral formulation which teach rapamycin formulations.*

One would be motivated to:

- *include citric acid/d,l-α-tocopherol in these formulations;*
- *find art teaching specific formulations of rapamycins, including CCI-779; and*
- *perfect a parenteral formulation of CCI-779 to reduce the bioavailability uncertainties of other forms of administration leading to more accurate and reproducible doses of the agent.*

Applicants respectfully request reconsideration of this rejection for the following reasons.

With respect, the Examiner's basis for combining these documents by her reference to *In re Aller* is incorrect. As the Examiner is aware, the "[c]laimed process

[at issue in *In re Aller*] which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%." Clearly, this case is not on point as related to the examined claims of this application. The reference process of *In re Aller* specified temperatures **and** acid concentrations which differed only slightly from the rejected temperatures and acid concentrations. These points differ substantially from the Examiner's basis for combining Skotnicki, Waranis, and Haeberlin.

As the Examiner noted, both Skotnicki and Waranis do not even utilize the term "antioxidant" or "d,l-α-tocopherol", let alone discuss any ranges for the same. The only discussion in Haeberlin related to "d,l-α-tocopherol" is in Examples 2 and 3 in which it is noted that 0.1% of the same is included. Haeberlin does not discuss any ranges for d,l-tocopherol. Therefore, *In re Aller* provides no basis for the Examiner's assertion that "...it is not inventive to discover the optimum or workable ranges by routine experimentation...".

Applicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims...In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range."[1] Further, "[a] particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation."[2] Applicants previously noted that the inclusion of d,l-α-tocopherol in Applicants' formulations is the result-effect variable. Further and contrary to the Examiner's assertion, Applicants presented the required showing that the use of **d,l-α-tocopherol** outside of the

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[1] MPEP §716.02-716.02(g) citing *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

[2] MPEP §214.05 citing *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

claimed range had negative effects including, without limitation, the generation of oxidative impurities. However, the Examiner disregarded this showing by noting that "...the instant claims do not specify the absence of oxidative impurities".[3] With respect, the pending claims are not required to recite every "advantage" provided by the claimed composition.

The Examiner also noted that although Haeberlin teaches rapamycin formulations containing 0.1% d,l-α-tocopherol, absolute alcohol, propylene glycol, Cremophor, and malonic acid, the "[s]ubstitution of CCI-779 for rapamycin and citric acid for malonic acid results in a formulation that anticipates or renders obvious instant claims 13-16 and 31-37".[4] In order to make this argument, the Examiner requires that one of skill in the art be led to remove the malonic acid of Haeberlin. Such motivation would be contrary to the teachings of Haeberlin. Not only do the formulations Haeberlin require an acid, but that the malonic acid component "...exhibits a pronounced stabilizing effect on the degradation of 40-O-(2-hydroxy)ethyl rapamycin and rapamycin".[5] Removing the acid component, particularly the preferred malonic acid component, from Haeberlin's formulations would be contrary to its teachings and destroy the advantages provided by the formulations described therein. Therefore, one of skill in the art would not be motivated to remove any acid from the formulation of Haeberlin and specifically the malonic acid as proposed by the Examiner.

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[3] Advisory Action dated June 8, 2009

[4] Ibid.

[5] Page 6, last paragraph of Haeberlin.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account No. 08-3040.

Respectfully submitted,

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